

**ATTACHMENT 1**  
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

RIEDL, Bernd, et. al.

Examiner: Delacroix Muirheir, Cybille

Serial No.: 10/086,417

Group Art Unit: 1614

Filed: March 4, 2007

Confirmation No.: 3172

Title: OMEGA-CARBOXY ARYL SUBSTITUTED DIPHENYL UREAS AS  
p38 KINASE INHIBITORS

**NON-RESPONSIVE AMENDMENT**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

To eliminate an obviousness type double patenting rejection in co-pending Application No. 09/899,227, kindly amend the above-identified application to cancel claim 12.

Amendments to the claims begin on page 2 of this paper.

Remarks/Arguments begin on page 16 of this paper.

## ATTACHMENT 1

This listing of claims will replace all prior versions, and listings, of claims in the application:

### Listing of Claims:

**Claim 1. (Previously presented)** A method of treating a condition mediated by p38 within a host, said method comprising administering to said host a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein

D is  $-NH-C(O)-NH-$ ,

A is a substituted moiety of up to 40 carbon atoms of the formula:  $-L-(M-L^1)_q$ , where L is a 5 or 6 membered cyclic structure bound directly to D,  $L^1$  comprises a substituted cyclic moiety having at least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3; and each cyclic structure of L and  $L^1$  contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur,

wherein  $L^1$  is substituted by at least one substituent selected from the group consisting of  $-SO_2R_x$ ,  $-C(O)R_x$  and  $-C(NR_y)R_z$ ,

$R_y$  is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo;

$R_z$  is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally

## ATTACHMENT 1

substituted by halogen;

$R_x$  is  $R_z$  or  $NR_aR_b$  where  $R_a$  and  $R_b$  are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

$-OSi(R_f)_3$  where  $R_f$  is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b)  $R_a$  and  $R_b$  together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of  $R_a$  or  $R_b$  is  $-C(O)-$ , a  $C_1-C_5$  divalent alkylene group or a substituted  $C_1-C_5$  divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted  $C_1-C_5$  divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or  $L^1$  is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and  $W_n$ , where n is 0-3;

wherein each W is independently selected from the group consisting of  $-CN$ ,  $-CO_2R^7$ ,  $-C(O)NR^7R^7$ ,  $-C(O)-R^7$ ,  $-NO_2$ ,  $-OR^7$ ,  $-SR^7$ ,  $-NR^7R^7$ ,  $-NR^7C(O)OR^7$ , -

## ATTACHMENT 1

$\text{NR}^7\text{C(O)R}^7$ ,  $-\text{Q}-\text{Ar}$ , and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of  $-\text{CN}$ ,  $-\text{CO}_2\text{R}^7$ ,  $-\text{C(O)R}^7$ ,  $-\text{C(O)NR}^7\text{R}^7$ ,  $-\text{OR}^7$ ,  $-\text{SR}^7$ ,  $-\text{NR}^7\text{R}^7$ ,  $-\text{NO}_2$ ,  $-\text{NR}^7\text{C(O)R}^7$ ,  $-\text{NR}^7\text{C(O)OR}^7$  and halogen up to per-halo; with each  $\text{R}^7$  independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{N(R}^7)-$ ,  $-(\text{CH}_2)_m-$ ,  $-\text{C(O)}-$ ,  $-\text{CH(OH)}-$ ,  $-(\text{CH}_2)_m\text{O}-$ ,  $-(\text{CH}_2)_m\text{S}-$ ,  $-(\text{CH}_2)_m\text{N(R}^7)-$ ,  $-\text{O}(\text{CH}_2)_m-$ ,  $\text{CHX}^a$ ,  $-\text{CX}^a_2-$ ,  $-\text{S}-(\text{CH}_2)_m-$  and  $-\text{N(R}^7)(\text{CH}_2)_m-$ , where  $m=1-3$ , and  $\text{X}^a$  is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by  $\text{Z}_{n1}$ , wherein  $n1$  is 0 to 3 and each Z is independently selected from the group consisting of  $-\text{CN}$ ,  $-\text{CO}_2\text{R}^7$ ,  $-\text{C(O)R}^7$ ,  $-\text{C(O)NR}^7\text{R}^7$ ,  $-\text{NO}_2$ ,  $-\text{OR}^7$ ,  $-\text{SR}^7$ ,  $-\text{NR}^7\text{R}^7$ ,  $-\text{NR}^7\text{C(O)OR}^7$ ,  $-\text{NR}^7\text{C(O)R}^7$ , and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of  $-\text{CN}$ ,  $-\text{CO}_2\text{R}^7$ ,  $-\text{COR}^7$ ,  $-\text{C(O)NR}^7\text{R}^7$ ,  $-\text{OR}^7$ ,  $-\text{SR}^7$ ,  $-\text{NO}_2$ ,  $-\text{NR}^7\text{R}^7$ ,  $-\text{NR}^7\text{C(O)R}^7$ , and  $-\text{NR}^7\text{C(O)OR}^7$ , with  $\text{R}^7$  as defined above.

**Claim 2. (Withdrawn)** A method as in claim 1 for the treatment of a cancerous cell growth mediated by p38 kinase.

**Claim 3. (Original)** A method as in claim 1 for the treatment of a disease other than cancer.

**Claim 4. (Original)** A method as in claim 1 wherein the condition within a host treated by administering a compound of formula I is rheumatoid arthritis, osteoarthritis, septic arthritis, tumor metastasis, periodontal disease, corneal ulceration, proteinuria, coronary thrombosis from atherosclerotic plaque, aneurysmal aortic, birth control, dystrophic epidermolysis bullosa, degenerative cartilage loss

## **ATTACHMENT 1**

following traumatic joint injury, osteopenias mediated by MMP activity, tempero mandibular joint disease or demyelating disease of the nervous system.

**Claim 5. (Withdrawn)** A method as in claim 1 wherein the condition within a host treated by administering a compound of formula I is rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (*Plasmodium falciparum* malaria and cerebral malaria), non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (demyelation and oligiodendrocyte loss in multiple sclerosis), advanced cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury/ toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft rejection (obliterative bronchitis) or complications due to total hip replacement.

**Claim 6. (Withdrawn)** A method as in claim 1 wherein the condition within a host treated by administering a compound of formula I is an infectious disease selected from the group consisting of tuberculosis, *Helicobacter pylori* infection during peptic ulcer disease, Chaga's disease resulting from *Trypanosoma cruzi* infection, effects of Shiga-like toxin resulting from *E. coli* infection, effects of enterotoxin A resulting from *Staphylococcus* infection, meningococcal infection, and infections from *Borrelia burgdorferi*, *Treponema pallidum*, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV).

## ATTACHMENT 1

**Claim 7. (Previously presented)** A method as in claim 1 wherein M is a bridging group which is one or more groups selected from the group consisting of -O-, -S-, -N(R<sup>7</sup>)-, -(CH<sub>2</sub>)<sub>m</sub>-, -C(O)-, -CH(OH)-, -(CH<sub>2</sub>)<sub>m</sub>O-, -(CH<sub>2</sub>)<sub>m</sub>S-, -(CH<sub>2</sub>)<sub>m</sub>N(R<sup>7</sup>)-, -O(CH<sub>2</sub>)<sub>m</sub>-CHX<sup>a</sup>-, -CX<sup>a</sup><sub>2</sub>-, -S-(CH<sub>2</sub>)<sub>m</sub>- or -N(R<sup>7</sup>)(CH<sub>2</sub>)<sub>m</sub>-, where m= 1-3, X<sup>a</sup> is halogen and R<sup>7</sup> is as defined in claim 1.

**Claim 8. (Original)** A method as in claim 7, wherein said substituted cyclic moiety L<sup>1</sup> is phenyl, pyridyl or pyrimidinyl.

**Claim 9. (Original)** A method of claim 1 wherein L<sup>1</sup> is substituted by -C(O)R<sub>x</sub> or -SO<sub>2</sub>R<sub>x</sub>, wherein R<sub>x</sub> is NR<sub>a</sub>R<sub>b</sub>.

**Claim 10. (Original)** A method of treating a disease mediated by p38 within a host, said method comprising administering to said host a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L<sup>1</sup>)<sub>q</sub>, where L is a 6 membered aryl moiety or a 6 membered hetaryl moiety bound directly to D, L<sup>1</sup> comprises a substituted cyclic moiety having at least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3; and each cyclic structure of L and L<sup>1</sup> contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to

### ATTACHMENT 1

D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur,

wherein  $L^1$  is substituted by at least one substituent selected from the group consisting of  $-SO_2R_x$ ,  $-C(O)R_x$  and  $-C(NR_y)R_z$ ,

$R_y$  is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo;

$R_z$  is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

$R_x$  is  $R_z$  or  $NR_aR_b$  where  $R_a$  and  $R_b$  are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

$-OSi(R_f)_3$  where  $R_f$  is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b)  $R_a$  and  $R_b$  together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of  $R_a$  or  $R_b$  is  $-C(O)-$ , a  $C_1-C_5$  divalent alkylene group or a

## ATTACHMENT 1

substituted C<sub>1</sub>-C<sub>5</sub> divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C<sub>1</sub>-C<sub>5</sub> divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L<sup>1</sup> is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W<sub>n</sub>, where n is 0-3;

wherein each W is independently selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>7</sup>, -C(O)NR<sup>7</sup>R<sup>7</sup>, -C(O)-R<sup>7</sup>, -NO<sub>2</sub>, -OR<sup>7</sup>, -SR<sup>7</sup>, -NR<sup>7</sup>R<sup>7</sup>, -NR<sup>7</sup>C(O)OR<sup>7</sup>, -NR<sup>7</sup>C(O)R<sup>7</sup>, -Q-Ar, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>7</sup>, -C(O)R<sup>7</sup>, -C(O)NR<sup>7</sup>R<sup>7</sup>, -OR<sup>7</sup>, -SR<sup>7</sup>, -NR<sup>7</sup>R<sup>7</sup>, -NO<sub>2</sub>, -NR<sup>7</sup>C(O)R<sup>7</sup>, -NR<sup>7</sup>C(O)OR<sup>7</sup> and halogen up to per-halo; with each R<sup>7</sup> independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is -O-, -S-, -N(R<sup>7</sup>)-, -(CH<sub>2</sub>)<sub>m</sub>-, -C(O)-, -CH(OH)-, -(CH<sub>2</sub>)<sub>m</sub>O-, -(CH<sub>2</sub>)<sub>m</sub>S-, -(CH<sub>2</sub>)<sub>m</sub>N(R<sup>7</sup>)-, -O(CH<sub>2</sub>)<sub>m</sub>-CHX<sup>a</sup>-, -CX<sup>a</sup><sub>2</sub>-, -S-(CH<sub>2</sub>)<sub>m</sub>- and -N(R<sup>7</sup>)(CH<sub>2</sub>)<sub>m</sub>-, where m= 1-3, and X<sup>a</sup> is halogen;

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z<sub>n1</sub>, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>7</sup>, -C(O)R<sup>7</sup>, -C(O)NR<sup>7</sup>R<sup>7</sup>, -NO<sub>2</sub>, -OR<sup>7</sup>, -SR<sup>7</sup>, -NR<sup>7</sup>R<sup>7</sup>, -NR<sup>7</sup>C(O)OR<sup>7</sup>, -NR<sup>7</sup>C(O)R<sup>7</sup>, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>7</sup>, -COR<sup>7</sup>, -C(O)NR<sup>7</sup>R<sup>7</sup>, -OR<sup>7</sup>, -SR<sup>7</sup>, -NO<sub>2</sub>, -NR<sup>7</sup>R<sup>7</sup>, -NR<sup>7</sup>C(O)R<sup>7</sup>, and -NR<sup>7</sup>C(O)OR<sup>7</sup>; and

wherein M is one or more bridging groups selected from the group consisting of -O-, -



### ATTACHMENT 1

S-, -N(R<sup>7</sup>)-, -(CH<sub>2</sub>)<sub>m</sub>-, -C(O)-, -CH(OH)-, -(CH<sub>2</sub>)<sub>m</sub>O-, -(CH<sub>2</sub>)<sub>m</sub>S-, -(CH<sub>2</sub>)<sub>m</sub>N(R<sup>7</sup>)-, -O(CH<sub>2</sub>)<sub>m</sub>- CHX<sup>a</sup>-, -CX<sup>a</sup><sub>2</sub>-, -S-(CH<sub>2</sub>)<sub>m</sub>- and -N(R<sup>7</sup>)(CH<sub>2</sub>)<sub>m</sub>-, where m= 1-3, X<sup>a</sup> is halogen and R<sup>7</sup> is as defined above.

**Claim 11. (Original)** A method of treating a disease mediated by p38 within a host, said method comprising administering to said host a compound of Formula I :



or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L<sup>1</sup>)<sub>q</sub>, where L is a substituted or unsubstituted phenyl or pyridine moiety bound directly to D, L<sup>1</sup> comprises a substituted phenyl, pyridine or pyrimidinyl moiety, M is a bridging group having at least one atom, q is an integer of from 1-3; and

B is a substituted or unsubstituted phenyl or pyridine group bound directly to D,

wherein L<sup>1</sup> is substituted by at least one substituent selected from the group consisting of -SO<sub>2</sub>R<sub>x</sub>-, -C(O)R<sub>x</sub> and -C(NR<sub>y</sub>)R<sub>z</sub>,

R<sub>y</sub> is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo;

R<sub>z</sub> is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R<sub>x</sub> is R<sub>z</sub> or NR<sub>a</sub>R<sub>b</sub> where R<sub>a</sub> and R<sub>b</sub> are

## ATTACHMENT 1

- a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

-OSi(R<sub>f</sub>)<sub>3</sub> where R<sub>f</sub> is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b) R<sub>a</sub> and R<sub>b</sub> together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R<sub>a</sub> or R<sub>b</sub> is -C(O)-, a C<sub>1</sub>-C<sub>5</sub> divalent alkylene group or a substituted C<sub>1</sub>-C<sub>5</sub> divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C<sub>1</sub>-C<sub>5</sub> divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L<sup>1</sup> is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W<sub>n</sub>, where n is 0-3;

wherein each W is independently selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>7</sup>, -C(O)NR<sup>7</sup>R<sup>7</sup>, -C(O)-R<sup>7</sup>, -NO<sub>2</sub>, -OR<sup>7</sup>, -SR<sup>7</sup>, -NR<sup>7</sup>R<sup>7</sup>, -NR<sup>7</sup>C(O)OR<sup>7</sup>, -NR<sup>7</sup>C(O)R<sup>7</sup>, -Q-Ar, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of -CN, -CO<sub>2</sub>R<sup>7</sup>, -

## ATTACHMENT 1

$C(O)R^7$ ,  $-C(O)NR^7R^7$ ,  $-OR^7$ ,  $-SR^7$ ,  $-NR^7R^7$ ,  $-NO_2$ ,  $-NR^7C(O)R^7$ ,  $-NR^7C(O)OR^7$  and halogen up to per-halo; with each  $R^7$  independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is  $-O-$ ,  $-S-$ ,  $-N(R^7)-$ ,  $-(CH_2)_m-$ ,  $-C(O)-$ ,  $-CH(OH)-$ ,  $-(CH_2)_mO-$ ,  $-(CH_2)_mS-$ ,  $-(CH_2)_mN(R^7)-$ ,  $-O(CH_2)_m-CHX^a-$ ,  $-CX^a_2-$ ,  $-S-(CH_2)_m-$  and  $-N(R^7)(CH_2)_m-$ , where  $m=1-3$ , and  $X^a$  is halogen;

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by  $Z_{n1}$ , wherein  $n1$  is 0 to 3 and each Z is independently selected from the group consisting of  $-CN$ ,  $-CO_2R^7$ ,  $-C(O)R^7$ ,  $-C(O)NR^7R^7$ ,  $-NO_2$ ,  $-OR^7$ ,  $-SR^7$ ,  $-NR^7R^7$ ,  $-NR^7C(O)OR^7$ ,  $-NR^7C(O)R^7$ , and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of  $-CN$ ,  $-CO_2R^7$ ,  $-COR^7$ ,  $-C(O)NR^7R^7$ ,  $-OR^7$ ,  $-SR^7$ ,  $-NO_2$ ,  $-NR^7R^7$ ,  $-NR^7C(O)R^7$ , and  $-NR^7C(O)OR^7$ ; with  $R^7$  is as defined above; and

wherein M is one or more bridging groups selected from the group consisting of  $-O-$ ,  $-S-$ ,  $-N(R^7)-$ ,  $-(CH_2)_m$ ,  $-C(O)-$ ,  $-CH(OH)-$ ,  $-(CH_2)_mO-$ ,  $-(CH_2)_mS-$ ,  $-(CH_2)_mN(R^7)-$ ,  $-O(CH_2)_m-CHX^a$ ,  $-CX^a_2-$ ,  $-S-(CH_2)_m-$  and  $-N(R^7)(CH_2)_m-$ , where  $m=1-3$ ,  $X^a$  is halogen and  $R^7$  is as defined above.

**Claim 12. (Canceled)**

**Claim 13-38 (Canceled)**

**Claim 39. (Withdrawn)** A method for the treatment of a disease mediated by p38 comprising administering a compound selected from the group consisting of:

N-(5-tert-butyl-2-methoxyphenyl)-N'-(4-(4-methoxy-3-(N-methylcarbamoyl)phenoxy)phenyl) urea,

N-(2-methoxy-5-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-

## ATTACHMENT 1

pyridyloxy)phenyl) urea,

N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea,

N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-N'-(3-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea and their pharmaceutically acceptable salts.

**Claim 40. (Withdrawn)** A method as in claim 39 comprising administering:

N-(5-tert-butyl-2-methoxyphenyl)-N'-(4-(4-methoxy-3-(N-methylcarbamoyl)phenoxy)phenyl) urea or a pharmaceutically acceptable salt thereof.

**Claim 41. (Withdrawn)** A method as in claim 39 comprising administering:

N-(2-methoxy-5-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea or a pharmaceutically acceptable salt thereof.

**Claim 42. (Withdrawn)** A method as in claim 39 comprising administering:

N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea or a pharmaceutically acceptable salt thereof.

**Claim 43. (Withdrawn)** A method as in claim 39 comprising administering:

N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea or a pharmaceutically acceptable salt thereof.

**Claim 44. (Withdrawn)** A method as in claim 39 comprising administering:

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-N'-(3-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea or a pharmaceutically acceptable salt

## ATTACHMENT 1

thereof.

**Claim 45. (Withdrawn)** A method as in claim 39 where the compound administered is a tosylate salt.

**Claim 46. (Withdrawn)** A method as in claim 40 where the compound administered is a tosylate salt.

**Claim 47. (Withdrawn)** A method as in claim 41 where the compound administered is a tosylate salt.

**Claim 48. (Withdrawn)** A method as in claim 42 where the compound administered is a tosylate salt.

**Claim 49. (Withdrawn)** A method as in claim 43 where the compound administered is a tosylate salt.

**Claim 50. (Withdrawn)** A method as in claim 44 where the compound administered is a tosylate salt.

**Claim 51. (Withdrawn)** A method for a treatment of the disease within a host selected from the group consisting of rheumatoid arthritis, osteoarthritis, septic arthritis, tumor metastasis, periodontal disease, corneal ulceration, proteinuria, coronary thrombosis from atherosclerotic plaque, aneurysmal aortic, birth control, dystrophic epidermolysis bullosa, degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, temporomandibular joint disease or demyelating disease of the nervous system said method comprising administering to a host a compound selected from the group consisting of:

N-(5-tert-butyl-2-methoxyphenyl)-N'-(4-(4-methoxy-3-(N-methylcarbamoyl)phenoxy)phenyl) urea,

N-(2-methoxy-5-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

### ATTACHMENT 1

N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea,

N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-N'-(3-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea and their pharmaceutically acceptable salts.

**Claim 52. (Withdrawn)** A method for a treatment of the condition within a host selected from the group consisting of rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (*Plasmodium falciparum* malaria and cerebral malaria), non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (demyelination and oligodendrocyte loss in multiple sclerosis), lymphoid malignancy, pancreatitis, impaired wound healing in infection, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury/ toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft rejection (obliterative bronchitis) or complications due to total hip replacement said method comprising administering to a host a compound selected from the group consisting of:

N-(5-tert-butyl-2-methoxyphenyl)-N'-(4-(4-methoxy-3-(N-methylcarbamoyl)phenoxy)phenyl) urea,

N-(2-methoxy-5-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

### ATTACHMENT 1

N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea,

N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-N'-(3-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea and their pharmaceutically acceptable salts.

**Claim 53. (Withdrawn)** A method for treating an infectious disease within a host selected from the group consisting of tuberculosis, Helicobacter pylori infection during peptic ulcer disease, Chaga's disease resulting from Trypanosoma cruzi infection, effects of Shiga-like toxin resulting from E. coli infection, effects of enterotoxin A resulting from Staphylococcus infection, meningococcal infection, and infections from Borrelia burgdorferi, Treponema pallidum, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV) said method comprising administering to a host a compound selected from the group consisting of:

N-(5-tert-butyl-2-methoxyphenyl)-N'-(4-(4-methoxy-3-(N-methylcarbamoyl)phenoxy)phenyl) urea,

N-(2-methoxy-5-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea,

N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-N'-(3-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea and their pharmaceutically acceptable salts.

**ATTACHMENT 1**  
**REMARKS**

The above amendment cancels claim 12 to eliminate an obviousness type double patenting rejection in a related application (Application No. 09/889,227) and is not responsive to the outstanding office action.

Respectfully submitted,

/Richard J. Traverso/

Richard J. Traverso, Reg. No. 30,595

Attorneys for Applicants

MILLEN, WHITE, ZELANO &  
BRANIGAN, P.C.  
Arlington Courthouse Plaza 1, Suite 1400  
2200 Clarendon Boulevard  
Arlington, Virginia 22201  
Telephone: (703) 243-6333  
FACSIMILE: (703) 243-6410

ATTORNEY

DOCKET NO.: BAYER -0016-P04

DATE: JULY 23, 2007